PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
99.1100 WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/09658	02/10/2000	30/09/1999
Applicant		
ORBUS MEDICAL TECHNOLOGIES INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT [redacted] 00/09658

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L33/10 A61L33/06 A61L27/34 A61L31/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
MEDLINE, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHNEIDER A ET AL: "An improved method for endothelial cell seeding on polytetrafluoroethylene small caliber vascular grafts." JOURNAL OF VASCULAR SURGERY, (1992 APR) 15 (4) 649-56., XP000884442 the whole document ---	1,2
A	EP 0 945 145 A (SHIMIZU YASUHIKO ;TAPIC INTERNATIONAL CO LTD (JP)) 29 September 1999 (1999-09-29) claims; example 1 ---	1-17
A	WO 95 31944 A (VEC TEC INC) 30 November 1995 (1995-11-30) claims; examples ---	1-17

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 2000	22/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax. (+31-70) 340-3016	ESPINOSA, M

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT [redacted] 00/09658

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No
A	WO 99 01167 A (MINNESOTA MINING & MFG) 14 January 1999 (1999-01-14) page 3, line 1 - line 5 ---	1-17
A	US 4 963 146 A (LI SHU-TUNG) 16 October 1990 (1990-10-16) claims ---	1-17
A	DATABASE WPI Section Ch, Week 198630 Derwent Publications Ltd., London, GB; Class D16, AN 1986-194636 XP002131679 & JP 61 128974 A (ADV KAIHATSU KENKYU), 17 June 1986 (1986-06-17) abstract -----	1,2

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/00/09658

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0945145 A	29-09-1999	US 6090117 A	18-07-2000
		CN 1237914 A	08-12-1999
		WO 9822155 A	28-05-1998
WO 9531944 A	30-11-1995	US 5643712 A	01-07-1997
		AU 2517395 A	18-12-1995
		AU 2595195 A	18-12-1995
		EP 0759692 A	05-03-1997
		WO 9531897 A	30-11-1995
		US 5699793 A	23-12-1997
		US 6024698 A	15-02-2000
WO 9901167 A	14-01-1999	US 6146771 A	14-11-2000
		AU 5166298 A	25-01-1999
		EP 1021216 A	26-07-2000
US 4963146 A	16-10-1990	US 5026381 A	25-06-1991
JP 61128974 A	17-06-1986	NONE	

PAT T COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 29 June 2001 (29.06.01)	
International application no. PCT/EP00/09658	Applicant's or agent's file reference 99.1100 WO
International filing date (day/month/year) 02 October 2000 (02.10.00)	**Priority date** (day/month/year) 30 September 1999 (30.09.99)
Applicant VAN DER GIESSEN, Wim et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

26 April 2001 (26.04.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Pascal Piriou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 April 2001 (05.04.2001)

PCT

(10) International Publication Number
WO 01/23016 A1

(51) International Patent Classification[7]: A61L 33/10, 33/06, 27/34, 31/10

(21) International Application Number: PCT/EP00/09658

(22) International Filing Date: 2 October 2000 (02.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99203203.7 30 September 1999 (30.09.1999) EP

(71) Applicant *(for all designated States except US)*: **ORBUS MEDICAL TECHNOLOGIES INC.** [US/US]; 5363 NW 35th Avenue, Fort Lauderdale, FL 33309 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VAN DER GIESSEN, Wim** [NL/NL]; Dr. Molenwaterplein 40, NL-3015 GD Rotterdam (NL). **VAN BEUSEKOM, Heleen** [NL/NL]; P.O. Box 1738, NL-3000 RD Rotterdam (NL).

(74) Agent: **VISSER-LUIRINK, Gesina**; Octrooibureau LIOC, P.O. Box 13363, NL-3507 LJ Utrecht (NL).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/23016 A1

(54) Title: INTRALUMINAL DEVICE, COATING FOR SUCH DEVICE, AND METHOD FOR PREPARING SAID DEVICE

(57) Abstract: Disclosed is an intraluminal device, suitable for implantation in a body. Said intraluminal device is provided with a coating which comprises: 50-97% heparan sulfate; 1-20% laminin; 0.2-15% type IV collagen. Furthermore a coating is disclosed, which coating is suitable for the above mentioned device, as well as a method for preparing such device, comprising the steps of: providing an intraluminal device for implantation in a body; preparing a composition, comprising, in about 50 mg/ml solvent: 50-97% heparan sulfate; 1-20% laminin; 0.2-15% type IV collagen; the solvent being a suitable buffer or water; dipping the intraluminal device in the composition; and drying the dipped intraluminal device.

Intraluminal device, coating for such device, and method for preparing said device

The present invention relates to an intraluminal device, suitable for implantation in a body, which intraluminal device is provided with a coating.

Intraluminal devices of the above mentioned type are generally known and applied. Such devices are for example applied in the treatment of blood vessel blockage in which the blocked blood vessel first is dilated, followed by placing a vascular prosthesis, in particular a stent, in the blood vessel in order to keep the vessel in the dilated state. This treatment does, however, give rise to several problems with regard to the vascular healing, as the natural healing process after such an operation is not regulated and as a consequence thereof undesirable local thrombosis can take place.

After the above implantation, the intraluminal device interacts with the vesselwall surface and the bloodstream. In a clinical setting the endothelialization of the intraluminal device is generally complete within two to three months after implantation. During this period the patient is at risk of thrombotic occlusion, undesired tissue growth, inflammation and vascular dysfunction.

There are several techniques available for controlling the above undesired effects of intraluminal devices, such as for example vascular stents. Thrombosis can passively be prevented by creating an inert surface which improves the surface characteristics that influence thrombosis. Such characteristics comprise, for example, charge, wettability and topography.

Thrombosis can also be prevented by binding one or more active components which inhibit thrombosis to the stent surface in order to actively prevent thrombosis. Examples of such components are prostaglandins, heparins, other thrombin inhibitors, or enzymes such as adenosine phosphatase.

Furthermore, thrombosis can be controlled by mimicking at the stent surface an already completed thrombotic response. This can be achieved by coating the stent surface with

fibrin, thereby creating a controlled thrombus in vitro, as polymerized and stabilised fibrin is no longer thrombogenetic.

Thrombus formation can also be limited by disguising the stent surface with plasma proteins such as albumin, gamma globulins or phospholipids, which causes the skipping of certain phases in the proteinaceous - thrombotic and cellular - response.

The above mentioned coatings have an anti-proliferative effect; the growth velocity is inhibited in order to prevent thrombosis or restenosis.

A coating consisting of an extract of an extracellular biologically active basement membrane composition, derived for instance from the Engelbreth-Holm-Swarm tumor has been described in US patent 4,829,000. However, it appears that this membrane is not suitable as a stent coating because it forms a thick shell on the stent surface.
A. Schneider et al, J. Vasc. Surgery 15, 649 (1992) describe the application of a coating consisting of fibronectin whereupon bovine corneal endothelial cells grow. The cells were said to produce an extracellular matrix, and removed after 14 days. Thus coated polymer material was seeded with bovine aortic endothelial cells.
However, also this coating has a proliferative effect, viz. a large growth velocity of the cells but a big chance on thrombosis too. Moreover, this procedure is complicated and may suffer from bio-contamination.

The present invention aims to provide for an intraluminal device according to the preamble which after implantation in a body adds to an improvement of the process of vascular healing and which prevents the formation of thrombosis, excessive tissue growth, inflammation and vascular dysfunction.

In order to achieve this the present invention is directed to an intraluminal device according to the preamble, which is characterised in that the coating comprises:

50-97% heparan sulfate;

1-20% laminin;

0.2-15% type IV collagen.

By providing an intraluminal device with a coating of the above specified composition a suitable substrate is provided on which endothelial cells can adhere. During the growth the endothelial cells create their own matrix upon which to grow and remain attached. Given that the normal endothelium is non-thrombogenic, providing a coating suitable for endothelial cell growth can shorten the period during which a patient is at risk of thrombotic occlusion.

All of the above components are also naturally present in the basement membrane of the blood vessel wall and are suitable for endothelial cell adhesion, growth and differentiation. Laminin can contribute to the binding properties of the coating to, for example DNA and RNA in gene therapy. Furthermore, type IV collagen adds to an improved attachment of the coating on the intraluminal device as well as a better attachment of the endothelial cells on the coated surface of the intraluminal device. Finally, the heparan sulfate is an important component as it has an effective anti-thrombogenic effect.

The coating according to the present invention provides a surface which is higher up in the natural healing cycle. The coating provides a fertile rich environment for endothelial cells and regulated thrombus formation. Thus, contrary to the coatings according to the prior art, the coating according to the present invention has a proliferative effect. As a result of the proliferative effect, the vascular wound healing is stimulated thereby decreasing the period during which thrombosis can occur and excessive tissue growth.

In a particular embodiment the coating comprises:

75-95% heparan sulfate;

3-10% laminin;

0.5-10% type IV collagen.

In a further preferred embodiment the coating comprises entactin and nidogen.

Said compounds add to the structural integrity of the coating and also improve the attachment of the - endothelial - cells to the intraluminal device coating.

In another advantageous embodiment the coating furthermore comprises a growth factor.

Growth factors in general stimulate the growth of - for example, endothelial - cells and therefore enhance the proliferative effect.

Preferably, the growth factor is chosen from the group consisting of bFGF, IGF, TGF-β and VEGF.

The different growth factors bFGF (basic fibroblast growth factor), IGF (insuline like growth factor), TGF-β (transforming growth factor-β), and VEGF (vascular endothelial growth factor) all add to the growth of specific components.

In order to prevent any risk of infection, the coating advantageously comprises an antibiotic.

In order to have an optimal effect the antibiotic should be a broad spectrum antibiotic, such as gentamycine.

In a preferred embodiment the coating of the intraluminal device according to the present invention comprises vitronectin.

Vitronectin offers a good basis for cell attachment; moreover it binds abciximab, GP 2b/3b inhibitor (ReoPro®) which is a compound with a known anti-thrombotic effect. By incorporating vitronectin in the intraluminal device coating and administering to a patient ReoPro® or other drugs that bind to vitronectin, thrombosis is even further prevented.

In a particular preferred embodiment of the intraluminal device according to the present invention, the coating comprises:

85-95% heparan sulfate;

5-6% laminin;

3-4% type IV collagen;

0.5-1.5% entactin and nidogen;

0.001-1% growth factors;

0.001-1% antibiotic.

In a preferred embodiment the intraluminal device comprises a vascular prosthesis such as a stent or a graft. The stent as well as the graft can be prepared from different materials known to the person skilled in the art.

The coated intraluminal device according to the present invention can furthermore be used as a basis for therapies such as, for example, drug delivery and gene therapy. Drugs can be bound to the coating such that the release thereof is controlled. As mentioned in the above, the presence of laminin in the coating improves the bonds which are desired and required in gene therapy. It is also possible to provide for one or more radioactive molecules in the coating in order to inhibit cell growth, if desired.

The present invention also relates to a coating suitable for application to an intraluminal device according to the present invention.

It will be clear that such coating may also be used on other substrates which can be implanted in a body.

The present invention also relates to a method for preparing an intraluminal device according to the above invention, comprising the steps of:

- providing an intraluminal device such as a wire of stainless steel, tantalum or polytetrafluoroethylene (PTFE) for implantation in a body;
- preparing a composition, comprising, in about 50 mg/ml solvent:

50-97% heparan sulfate;

1-20% laminin;

0.2-15% type IV collagen;

the solvent being a suitable buffer or water;

- dipping the intraluminal device in the composition; and

- drying the dipped intraluminal device.

The method as such is very simple and easy to perform and moreover is not time-consuming. The drying step can take place with or without heated or forced air drying.

Preferred embodiments of the method according to the present invention are those wherein the compositions to be prepared furthermore comprise one or more of the group consisting of a growth factor such as bFGF, IGF, TGF-β and VEGF, an antibiotic and vitronectin.

Preferably, a method for preparing a intraluminal device according to the above particular preferred embodiment, comprising the steps of:

- providing an intraluminal device such as a wire of stainless steel, tantalum or polytetrafluoroethylene (PTFE) for implantation in a body;

- preparing a composition, comprising, in about 50 mg/ml solvent:

85-95% heparan sulfate;

5-6% laminin;

3-4% type IV collagen;

0.5-1.5% entactin and nidogen;

0.001-1% growth factors;

0.001-1% antibiotic;

the solvent being a suitable buffer or water;

- dipping the intraluminal device in the composition; and

- drying the dipped intraluminal device.

The present invention will be illustrated by the following, in no way the invention limiting, example.

Example

Helical coil, tantalum coronary stents were coated with the matrigel (n=2) as described in US patent 4,829,000 or with a coating according to the present invention (n=2).
The stents were percutaneously implanted using sterile techniques in coronary arteries of farm-bred Yorkshire swines (ca. 30 kg) in such a way that one of each stent was placed per animal.
One of the two matrigel coated stents showed thrombotic occlusion within one week. The stent coated according to the present invention in the same animal was in a good condition at autopsie. Mean neointimal thickness at one week was 24 μm (range 20 - 44 μm) in the matrigel coated stent and 14 μm (range 10 - 24 μm) in the stent coated according to the present invention.
In vitro platelet aggregation was measured in fresh, heparinized blood by measuring the impedance between the two electrodes. For this study the electrodes itself were coated with either matrigel or with the coating according to the present invention. Matrigel coating caused a decrease in impedance of 40 % compared to a bare electrode. The coating with a composition according to the present invention caused a decrease of 60 %. This implies a reduction of platelet aggregation in whole blood of the coating according to the present invention.

Claims

1. Intraluminal device, suitable for implantation in a body, which device is provided with a coating, characterised in that the coating comprises:

50-97% heparan sulfate;

1-20% laminin;

0.2-15% type IV collagen.

2. Intraluminal device according to claim 1, characterised in that the coating comprises:

75-95% heparan sulfate;

3-10% laminin;

0.5-10% type IV collagen.

3. Intraluminal device according to claim 1 or 2, characterised in that the coating comprises entactin and nidogen.

4. Intraluminal device according to claim 1-3, characterised in that the coating furthermore comprises a growth factor.

5. Intraluminal device according to claim 4, charaterised in that the growth factor is chosen from the group consisting of bFGF, IGF, TGF-β and VEGF.

6. Intraluminal device according one or more of the preceding claims, characterised in that the coating comprises an antibiotic.

7. Intraluminal device according to claim 6, characterised in that the antibiotic comprises gentamycine.

8. Intraluminal device according to one or more of the preceding claims, characterised in that the coating comprises vitronectine.

9. Intraluminal device according to one or more of the preceding claims, characterised in that the coating comprises:

85-95% heparan sulfate;

5-6% laminin,;

3-4% type IV collagen;

0.5-1.5% entactin and nidogen;

0.001-1% growth factors;

0.001-1% antibiotic.

10. Intraluminal device according to one or more of the preceding claims, characterised in that the prosthesis comprises a stent or a graft.

11. Coating suitable for a intraluminal device according to one or more of the preceding claims 1-10.

12. Method for preparing a intraluminal device according to one or more of the claims 1-10, comprising the steps of:

- providing a intraluminal device for implantation in a body;
- preparing a composition, comprising, in about 50 mg/ml solvent:

50-97% heparan sulfate;

1-20% laminin;

0.2-15% type IV collagen;

the solvent being a suitable buffer or water;

- dipping the intraluminal device in the composition; and
- drying the dipped intraluminal device.

13. Method according to claim 12, characterised in that the composition comprises entactin and nidogen.

14. Method according to claim 12 or 13, characterised in that the composition furthermore comprises a growth factor, chosen from the group consisting of bFGF, IGF, TGF-β and VEGF.

15. Method according to one or more of claims 12-14, characterised in that the composition comprises an antibiotic.

16. Method according to one or more of claims 12-15, characterised in that the composition comprises vitronectin.

17. Method according to one or more of the claims 12-16, characterised in that the composition comprises:

85-95% heparan sulfate;

5-6% laminin;

3-4% type IV collagen;

0.5-1.5% entactin and nidogen;

0.001-1% growth factors;

0.001-1% antibiotic.

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Intern... Application No
PCT/EP 00/09658

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0945145 A	29-09-1999	US 6090117 A	18-07-2000
		CN 1237914 A	08-12-1999
		WO 9822155 A	28-05-1998
WO 9531944 A	30-11-1995	US 5643712 A	01-07-1997
		AU 2517395 A	18-12-1995
		AU 2595195 A	18-12-1995
		EP 0759692 A	05-03-1997
		WO 9531897 A	30-11-1995
		US 5699793 A	23-12-1997
		US 6024698 A	15-02-2000
WO 9901167 A	14-01-1999	US 6146771 A	14-11-2000
		AU 5166298 A	25-01-1999
		EP 1021216 A	26-07-2000
US 4963146 A	16-10-1990	US 5026381 A	25-06-1991
JP 61128974 A	17-06-1986	NONE	

INTERNATIONAL SEARCH REPORT

Interr[redacted] Application No
PCT/EP 00/09658

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 01167 A (MINNESOTA MINING & MFG) 14 January 1999 (1999-01-14) page 3, line 1 - line 5	1-17
A	US 4 963 146 A (LI SHU-TUNG) 16 October 1990 (1990-10-16) claims	1-17
A	DATABASE WPI Section Ch, Week 198630 Derwent Publications Ltd., London, GB, Class D16, AN 1986-194636 XP002131679 & JP 61 128974 A (ADV KAIHATSU KENKYU), 17 June 1986 (1986-06-17) abstract	1,2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
99.1100 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/09658	02/10/2000	30/09/1999

International Patent Classification (IPC) or national classification and IPC
A61L33/10

Applicant
ORBUS MEDICAL TECHNOLOGIES INC.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26/04/2001	04.09.2001
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Bochelen, D Telephone No. +49 89 2399 8150

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09658

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-7 as originally filed

Claims, No.:

1-17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL SEARCH REPORT

Intern[illegible] Application No
PCT/EP 00/09658

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L33/10 A61L33/06 A61L27/34 A61L31/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
MEDLINE, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHNEIDER A ET AL: "An improved method for endothelial cell seeding on polytetrafluoroethylene small caliber vascular grafts." JOURNAL OF VASCULAR SURGERY, (1992 APR) 15 (4) 649-56., XP000884442 the whole document ---	1,2
A	EP 0 945 145 A (SHIMIZU YASUHIKO ;TAPIC INTERNATIONAL CO LTD (JP)) 29 September 1999 (1999-09-29) claims; example 1 ---	1-17
A	WO 95 31944 A (VEC TEC INC) 30 November 1995 (1995-11-30) claims; examples ---	1-17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 2000	22/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ESPINOSA, M

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Form PCT/ISA/210 (second sheet) (July 1992)

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-17
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document:

D1: SCHNEIDER A ET AL: 'An improved method for endothelial cell seeding on polytetrafluoroethylene small caliber vascular grafts.' JOURNAL OF VASCULAR SURGERY, (1992 APR) 15 (4) 649-56., XP000884442

2. **Novelty and Inventive step (Article 33 (1) (2) and (3) PCT)**:

Document D1, which is considered to be the most relevant prior art, discloses the coating of vascular grafts with an extracellular matrix comprising laminin, collagen, heparan sulfate and endothelial cell growth factors, which is deposited by corneal cells cultivated on the surface of the graft. The subject-matter of **claims 1, 11 and 12** differs in the intraluminal device is coated by dipping it in a solution comprising heparan sulfate, laminin and type IV collagen at specific concentrations. The coating according to the invention avoids the drawbacks of the coating according to D1, i.e. complexity of the coating process, risk of thrombosis and bioconta-mination. Moreover, as shown in the example the coating according to the invention shows better anti-thrombogenic activity than other ECM coating. Consequently, it is considered that the subject-matter of **claims 1, 11 and 12** is new and involves an inventive step. The dependent **claims 2-9, 13-17** as well fulfill the requirements of Article 33 PCT.